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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/310,685	05/04/1999	JONATHAN ROBERT LAMB	674525-2001	9186

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EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	29

DATE MAILED: 09/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/310,685	Applicant(s) LAMB ET AL.	
	Examiner F. Pierre VanderVegt	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *48-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *48-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The Examiner in charge of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to F. Pierre VanderVegt, Ph.D. in Art Unit 1644.

This application is a continuation-in-part of PCT/GB97/03058.

Claims 1-47 have been canceled previously.

Claims 48-51 are currently pending and are the subject of examination in the present Office Action.

1. The following represent new grounds of rejection and objection and result in the present Office Action being made **Non-Final**. Applicant's arguments filed June 4, 2003 have been considered but are moot in view of the new ground of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing T cell activation for allergic conditions and some graft rejection using the DSL domain containing Notch ligands Serrate and Delta, does not reasonably provide enablement for reducing T cell activation for autoimmune conditions or the full spectrum of "graft rejection." The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to the reduction of T cell activation via administration of the Notch ligands Serrate (claims 48-49) and Delta (50-51). Claims 49 and 51 further recite that the reduction of T cell activation is in the treatment of allergy, autoimmunity and graft rejection.

The specification is not enabled for the full scope of what is encompassed by the term "graft rejection." The declaration of Margaret J. Dallman filed August 22, 2002 demonstrates that recombinant expression of Delta by antigen presenting cells *in vivo* modulated the response of the host to allogeneic L

cells and allogeneic heart grafts. However, neither the specification nor the declaration suggests success with grafts of other types, as the mechanism of rejection is known in the art to be different for different types of tissue. For example, Jones et al. (J. Immunol. (2001) 166:2824-2830; U1 on form PTO-892) discloses that heart, skin and pancreatic islet tissue are differentially susceptible to T cell-mediated allograft rejection (see entire publication, Abstract in particular). In fact, Jones discloses that "a well-established hierarchy exists among organ and tissue allografts in their susceptibility to rejection" and that skin, small bowel, and lung are more difficult to induce acceptance of than heart kidney and liver (page 2824, first column in particular). Tufveson et al. (Immunol. Rev. (1993) 136:99-109; V1 on form PTO-892) discloses that cardiac grafting in rodents is the most commonly used technique to test immunosuppressants, but "[*a*] *main problem in the rodent model is the ease with which rejection is usually supressed* (page 100 in particular; emphasis in original). Accordingly, one skilled in the art would not be able to predict what types of tissue would have a reduced incidence of graft rejection due to Delta or Serrate administration based upon the paucity of guidance provided by the instant specification. Similarly, autoimmune diseases are well known in the art to be differentially mediated by different T cell subsets or B cells (via humoral means), as well as differentially regulated. There is no showing by specification or by any of the declarations that an example of the modulation of an autoantigen can be effected through administration of a DSL domain protein, only that Delta and Serrate can modulate the response to a foreign antigen, such as ovalbumin. Accordingly, based upon the disclosure of the instant specification, the artisan would not be able to predict that any condition encompassed by the term "autoimmunity" would be able to be modulated via a reduction of T cell activation by Serrate or Delta administration.

In view of the breadth of the claims, the limited working examples, the state of the art, the level of predictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

3. Claims 48-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reduction of T cell activation via administration of Serrate- or Delta-expressing recombinant cells or of F_c-conjugated Delta or Serrate, does not reasonably provide enablement for reduction of T cell activation via administration of Delta or Serrate by any other means. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Briefly, the claims are most broadly drawn to the treatment of a patient and the *in vivo* reduction of T cell activation by the administration of Delta or Serrate by any means. However, the specification does not provide any expectation of success in affecting *in vivo* T cell activation via any means other than enhanced expression on the surface of antigen presenting cells or by the administration of Delta or Serrate peptides which have been fused to an immunoglobulin F_c domain peptide. Example 2 of the instant specification discloses the production of a fusion protein comprising the extracellular domain of Delta fused to an immunoglobulin Fc domain, however the specification does not disclose in vivo administration of the fusion construct. The fusion construct is only disclosed by the declaration filed August 22, 2002 by Brian R. Champion. It is well known in the art that antigen presenting cells (APC) bear F_c receptors. Therefore, APCs can capture the fusion protein and potentially display the Delta extracellular domain on their surface. Examples 4-10 each disclose an example where antigen presenting cells (examples 4-6, 8 and 9) or T cells (examples 7 and 10) have been modified extracorporeally and administered to hosts, affecting the *in vivo* responses to foreign antigens. In addition, the declarations of Margaret J. Dallman and Jonathan E Lamb, both filed August 22, 2002, are dependent upon the use of antigen presenting cells that recombinantly express Delta or Serrate as a constitutive surface protein. Accordingly, the present specification only provides a reasonable expectation of success where the Delta or Serrate is administered in such a manner where it can be expressed on the surface of an APC or T cell. The artisan would not be able to reasonably predict, based upon the guidance provided by the instant specification, that Delta or Serrate administration to a patient in a manner that does not result in the extracellular domain of the protein on the surface of an APC or T cell would be effective in the *in vivo* reduction of T cell activation and the modulation of a condition in said patient.

In view of the breadth of the claims, the limited working examples, the state of the art, the level of predictability of the art, and the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

Conclusion

4. No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (703) 305-4441. The examiner can normally be reached on M-Th 6:30-4:00; Alternate Fridays 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

F. Pierre VanderVegt, Ph.D
Patent Examiner
September 23, 2003

PHILLIP GAMBEL, PH.D
PRIMARY EXAMINER